Antithrombotic Therapy for Venous Thromboembolic Disease

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Abbreviations: APTT = activated partial thromboplastin time; DVT = deep venous thrombosis; HIT = heparin-induced thrombocytopenia; INR = international normalized ratio; IPG = impedance plethysmography; LMW = low molecular weight; PE = pulmonary embolism; PTE = pulmonary thromboendarterectomy; TCT = thrombin clotting time; tPA = tissue plasminogen activator (alteplase); VTE = venous thromboembolism

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Stasis of blood, abnormalities of the vessel wall, and changes in the soluble and formed elements of the blood are the major contributors to thrombosis. All of these alterations can contribute to venous thrombosis, depending on the specific risk factors that are present in a given patient.

Antithrombotic regimens modify one or more of these abnormalities. These regimens include drugs that inhibit blood coagulation, such as the various heparins and heparinoids; warfarin; direct thrombin inhibitors; drugs that inhibit platelet function, such as aspirin and dextran; and techniques that counteract venous stasis, such as compression stockings and pneumatic compression devices. In this broad sense, thrombolytic agents are also antithrombotic (Table 1). This section will describe the effectiveness of antithrombotic agents in the treatment of venous thromboembolism (VTE), a disease that encompasses both deep venous thrombosis (DVT) and pulmonary embolism (PE). Several of these agents are also useful for the primary prevention of VTE, and this application of antithrombotic therapy is reviewed in the preceding chapter.

All antithrombotic therapy with either anticoagulants or platelet-active drugs is prophylactic, since these agents interrupt progression of the thrombotic process; but unlike thrombolytic agents, they do not as a rule actively resolve it. Unfractionated heparin, low-molecular-weight (LMW) heparin, thrombolytic agents, and warfarin are used to treat venous thromboembolic disease.

1. Treatment of VTE

1.1. Effective Regimens

Treatment regimens for DVT and PE are similar because the two conditions are manifestations of the same disease process. When patients with VTE are carefully studied, the majority of those with proximal DVT also have PE (symptomatic or asymptomatic) and *vice versa*. Furthermore, clinical trials in patients with DVT alone have validated treatment regimens that are similar to regimens used in patients with both DVT and PE and in patients known to have only PE. None of these studies established the superiority of a treatment regimen for patients with PE in stable condition that was substantially different than regimens for patients with DVT. Patients with VTE who receive adequate anticoagulation generally do not die of recurrent disease. However, it should be noted that patients who are treated for PE are almost four times more likely (1.5% vs 0.4%) to die of recurrent VTE in the next year than are patients who are treated for DVT.[1] The major exception to the statement that the two conditions are treated similarly is that patients with symptomatic proximal DVT may benefit from fitted compression stockings for at least 3 months to reduce the incidence of the postthrombotic syndrome.[2]

Heparin: Heparin, an acidic glycosaminoglycan, is a time-honored and relatively effective antithrombotic agent, but it requires careful monitoring and dose adjustment when used to treat active disease. Clinical preparations vary over a molecular weight range of 5,000 to 30,000 d, with a mean molecular weight of approximately 15,000 d. The drug acts by catalyzing the effect of a plasma inhibitor, antithrombin III, so that the inhibitor more efficiently combines with and inactivates a number of serine proteinases, notably thrombin (factor IIa), factor Xa, and factor IXa. Heparin also acts to inhibit activation of factors V and VIII by thrombin.[3,4] Neither hepatic nor renal disease seem to interfere notably with the clearance of the drug at therapeutic concentrations.[5] Heparin is currently obtained from the gut mucosa of animals and is available as a sodium or calcium salt.

The unit of heparin is measured in animals using a biological assay. Unitage may vary as much as 50% on a weight basis; consequently, heparin is properly prescribed by units, not weight.

Heparin has proved effective in the treatment of PE and DVT.[6] The first and only trial that incorporated an untreated group with PE was completed before the advent of perfusion lung scanning and pulmonary angiography and has several other flaws. The much higher mortality (25%) in the untreated patients, combined with a demonstration of autopsy-verified PE as the cause of death, is persuasive. Subsequent studies[7,8] have attested to the reduced mortality rate when heparin was used to treat VTE disease, and to the high mortality when patients with PE did not receive anticoagulant therapy.[9] Recent randomized clinical trials[10–16] have confirmed the efficacy of continuous IV heparin in the treatment of DVT. Other trials indicate that subcutaneous heparin is adequate initial therapy for DVT, provided that activated partial thromboplastin time (APTT) is prolonged into the therapeutic range or that adequate doses are used.[17–19]

Clinical trials have also shown the efficacy of heparin and warfarin in treating symptomatic calf vein thrombosis.[20,21] Venous thrombosis that remains confined to the deep calf veins appears to be associated with a low risk of clinically important PE. In patients with asymptomatic calf vein DVT, serial testing with impedance plethysmography

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Table 1—*Antithrombotic Agents in VTE

Agents	Mechanism of Action*	Onset of Action	Application	Usual Route of Administration	Contraindications
Heparin	With ATIII, prevents thrombin activity (anti-IIa) and to a lesser extent thrombin generation (anti-Xa)	Immediate	Prevention and treatment of VTE	IV or subcutaneous	Severe active bleeding; documented hypersensitivity; HIT
LMW heparins and heparinoids	With ATIII, inhibits thrombin generation by an effect on Xa, to a lesser extent on IIa	Immediate	Prevention and treatment of VTE	Subcutaneous	Severe active bleeding; documented hypersensitivity; HIT
Hirudin and direct thrombin inhibitors	Inhibits thrombin activity directly	Immediate	Prevention and treatment of VTE; treatment of HIT	IV	Severe active bleeding
Warfarin	Inhibits proper synthesis of vitamin K-dependent coagulation factors (II, VII, IX, X)	4 to 5 d	Long-term treatment of VTE; prevention of VTE	Oral	Severe active bleeding; pregnancy; documented hypersensitivity
Streptokinase	Activates plasminogen, dissolves fibrin; degrades fibrinogen and several other plasma proteins	Immediate	Treatment of severe or life-threatening PE or DVT	IV	Active bleeding; recent surgery; stroke; or severe trauma; any hemorrhagic disease; recent streptococcal infection or treatment with streptokinase documented hypersensitivity
Urokinase	Activates plasminogen, dissolves fibrin; degrades fibrinogen and several other plasma proteins	Immediate	Treatment of severe or life-threatening PE or DVT	IV	Active bleeding; recent surgery; severe trauma; any hemorrhagic disease
Alteplase	Activates plasminogen bound to fibrin; dissolves fibrin	Immediate	Treatment of severe or life-threatening PE or DVT	IV	Active bleeding; intracranial pathologic condition; recent surgery; severe trauma; any hemorrhagic disease
Reteplase	Activates plasminogen bound to fibrin; dissolves fibrin	Immediate	Treatment of severe or life-threatening PE or DVT	IV	Active bleeding; intracranial pathologic condition; recent surgery; severe trauma; any hemorrhagic disease

*ATIII - antithrombin III

(IPG) or duplex ultrasound for 10 to 14 days appears to be effective for identifying patients with extending calf DVT; normal findings by serial IPG or ultrasound are associated with a low risk of clinically important PE (< 1%) or recurrent venous thrombosis (2%). Patients with extending calf vein DVT, although asymptomatic, should probably be treated. Most patients with symptomatic calf vein thrombosis should receive anticoagulant therapy. An alternate approach is to follow up the patient with serial IPG or ultrasound to separate the 20% of patients who develop proximal extension (and require treatment) from the remaining 80% of patients who do not, in whom the risks of anticoagulant therapy may outweigh the benefits (*eg*, in patients at high risk of bleeding).[20] In contrast, superficial thrombophlebitis in the absence of DVT is generally treated effectively with nonsteroidal anti-inflammatory agents. However, it is necessary to perform duplex ultrasonography to be certain that DVT does not exist concurrently with superficial thrombophlebitis.[22]

Heparin Dose and Bleeding: Plasma levels during administration of heparin are not easily predictable,[5,23,24] and more specific assays for the drug have not been widely applied.[25] The lack of a clear relationship between heparin dose and bleeding probably results from the variable interference of heparin with platelet and endothelial cell function in patients.[26–28] Please see the chapter on "Heparin and Low-Molecular-Weight Heparin: Mechanisms of Action, Pharmacokinetics, Dosing Considerations, Monitoring, Efficacy, and Safety" for details on the complex interaction of heparin dose, anticoagulation intensity, and bleeding.

Relationship Between Risk of Bleeding and Method of Administering Heparin: Six randomized studies[29–34] compared the bleeding and thromboembolic recurrence rates when heparin was administered by intermittent IV injection or by continuous IV infusion. Two studies[29,30] reported that continuous heparin infusion was associated

with a lower frequency of bleeding (1% and 0% compared with 9% and 33%), and the third study[31] reported the trend toward reduced bleeding with continuous heparin, 5% compared with 10%. In the fourth study,[32] there was a trend in the other direction. The other two studies[33,34] were too small to draw clear conclusions about recurrence rates. Patients receiving continuous-infusion heparin, however, also received a lower dose of heparin. Therefore, it is uncertain whether the difference noted in the rates of bleeding between patients randomized to continuous IV infusion or intermittent IV injection is related to the method of heparin administered or to the difference in the total dose of heparin given to the two groups.

Only one randomized trial[30] evaluated the benefit of monitoring heparin therapy. In this study, patients received intermittent heparin injections, either with or without laboratory control using the APTT. There was no significant difference detected in the frequency of bleeding between the two groups (8% vs 10%), suggesting that when heparin is administered by intermittent injection, monitoring the response may not reduce the risk of bleeding.

Relationship Between Heparin Levels and Thrombus Inhibition: It is generally accepted that a minimum level of heparin anticoagulation must be maintained to achieve an effective antithrombotic state[10,11,34–37] and that inadequate anticoagulant therapy results in unacceptably higher rates of recurrent thromboembolism. Animal experiments support the concept that a plasma level of heparin between 0.2 IU/mL and 0.4 IU/mL (measured by protamine sulfate titration) is necessary to interrupt an ongoing thrombotic process.[38–41] The most widely used test for monitoring heparin therapy is the APTT, which is a global coagulation test and does not directly reflect plasma heparin levels.[33,42,43] Inadequate initial heparin therapy seems to increase the long-term recurrence rate despite adequate long-term treatment.[44] A retrospective analysis published 3 decades ago suggested that recurrent VTE is infrequent if continuous IV heparin is administered in doses adjusted to prolong the APTT > 1.5 times the control value.[35] An analysis of a randomized, prospective trial[10] comparing IV and subcutaneous heparin administration in patients with proximal vein thrombosis demonstrated that failure to achieve an adequate anticoagulant response (APTT > 1.5 times control) is associated with a high risk (20 to 25%) of recurrent VTE. In that study,[10] the control APTT value was defined as the mean APTT obtained from pooled plasma of normal volunteers. An analysis[45] of three consecutive double-blind trials supports this observation. In general, an APTT > 1.5 times control or mean normal corresponded to a blood heparin level of 0.2 IU/mL in these studies. However, other analyses[46–48] of clinical trial results suggest that the risk of recurrence depends also on the heparin dose itself. Clinical recurrence is unusual as long as heparin is infused IV in a dose of at least 1,250 U/h.[45]

The APTT does not always correlate reliably with plasma heparin levels or with antithrombotic activity. The APTT can be shortened by increased levels of various plasma proteins and clotting factors such as factor VIII, which is an acute-phase reactant, and the anticoagulant effect of heparin can be suppressed by variable concentrations of heparin-binding proteins in plasma.[49] Moreover, the APTT is dependent on the coagulation timer and reagents used to perform the test.[50] Consequently, clinicians are often perplexed by patients with acute thrombosis who require large amounts of heparin (> 40,000 U/d) but do not have "therapeutic" clotting times and occasionally by patients who seem to have therapeutic times and yet suffer recurrent thrombotic events.

LMW heparins should obviate some of these problems because these products have a more predictable dose-response relationship when administered on the basis of body weight. These agents can be used to treat many patients with acute DVT without the need for subsequent monitoring or dose adjustment. When one considers the global costs of treating VTE, LMW heparins are cost-effective.[51–55] However, LMW heparins have only recently come into use in North America, largely for treatment of acute DVT. Given the current period of transition from one treatment method to another, it is important to optimize management protocols for unfractionated heparin as well as to develop new protocols for LMW heparin.

Both animal and human studies have shown that a plasma heparin level in the range of 0.2 to 0.4 IU/mL (protamine sulfate titration) inhibits thrombus propagation.[38–41,56] This hypothesis was tested in a controlled clinical trial[56] in which patients with acute VTE who required large doses of heparin (> 35,000 U/d) were randomized to either continued APTT monitoring or direct monitoring of blood heparin levels. Subsequent dosage adjustments were made according to the monitoring test employed. Patients whose heparin level was monitored directly required less heparin than did patients receiving APTT monitoring. Outcome differences between the two groups were statistically insignificant, although trends favored decreased recurrent thromboembolism and bleeding in the group monitored by plasma heparin levels. Measuring plasma heparin levels rather than the APTT is probably more appropriate to monitor and dose-adjust heparin in the treatment of acute thrombosis, but this approach should be validated in larger studies.

Unfortunately, many hospital laboratories are not prepared to monitor heparin levels directly and expeditiously report the results, although automated assays for heparin levels show promise.[57] A practical compromise is prospective determination in each laboratory of the therapeutic range of the APTT in seconds that corresponds to plasma heparin levels from 0.2 to 0.4 IU/mL by protamine sulfate titration or 0.3 to 0.6 IU/mL by an amidolytic assay. This correlation should preferably be done *ex vivo* using plasma specimens from at least 30 to 40 patients receiving heparin therapy. If it can be shown that the therapeutic range established *ex vivo* is similar to that established *in vitro* by using plasma specimens spiked with known concentrations of heparin, the latter method, which is more practical and less expensive, may be used. If the conditions of the APTT change, *eg*, use of a new APTT reagent or reagent batch, new coagulation timer, or heparin preparation, then the therapeutic range for heparin must be reestablished.

Given the continued lack of an international reference APTT reagent preparation that would allow development of a normalized ratio system for heparin analogous to the international normalized ratio (INR) for warfarin, establishing the therapeutic range in each laboratory as described above is recommended as a way to standardize heparin therapy at this time.

An alternative to the APTT is the thrombin clotting time (TCT). This assay is easily performed, has a rapid turnaround time, and is linear in seconds between plasma heparin levels of 0.2 to 0.6 U, which includes the therapeutic range of heparin.[58] The TCT has greater specificity than the APTT in predicting heparin levels, is more reproducible, and is not affected as much by warfarin.[59–61] The TCT may be shortened when antithrombin levels are low,[62] and fibrinogen levels < 100 mg/dL may prolong the test by several seconds. As with the APTT, plasma heparin levels should first be correlated with the TCT *ex vivo* before the test is used clinically.

Heparin is cleared rapidly from the plasma, with an average half-life of < 60 min when given in therapeutic doses.[63,64] Audits of heparin therapy indicate that the current clinical practice of intuitive ordering of heparin often results in inadequate anticoagulation, probably because of fear of bleeding.[65–67] The importance of exceeding the lower limit of the therapeutic range has been strongly supported by findings of prospective clinical trials. Indeed, firm evidence indicates that failure to exceed the lower limit is associated with unacceptably high rates of recurrent VTE.[44,45,63]

In the first few days of heparin therapy, a weak association exists between supratherapeutic APTT responses and bleeding, which is in direct contrast to the clear association between subtherapeutic APTT responses and recurrent VTE.[10,11,44,45] Several nomograms have been published[66–68] to aid the clinician in reaching and maintaining the therapeutic range with heparin anticoagulation. All of these approaches are based on frequent monitoring of the APTT in the first few days of therapy and rapid response to subtherapeutic or supratherapeutic values for the APTT. In this regard, when the APTT is too low, one can raise the blood level of heparin quicker by giving another bolus and increasing the constant infusion rate simultaneously. Conversely, when the APTT is too prolonged, the heparin infusion can be discontinued for a short time not to exceed 1 h. Table 2 gives a weight-based nomogram[67] that has been widely employed for dosing and adjusting therapy.

Perhaps the most common mistake with heparin dosing is the choice of an inadequate maintenance dose. Whether the heparin dose is calculated on a body weight basis or not, the average daily maintenance dose is generally > 30,000 IU (18 U × 70 kg × 24 h = 30,240 IU).[10,69,70] When unfractionated heparin is given subcutaneously as an initial anticoagulating dose, therapy should begin with a small IV loading dose (3,000 to 5,000 U) followed by 17,500 U (or 250 IU/kg) subcutaneously q12h.[18] The dose should then be adjusted to give an APTT that corresponds to a plasma heparin level of 0.2 IU/mL within 1 h of the next scheduled subcutaneous dose. Heparin requirements are usually greatest in the first few days after the acute thromboembolic event[5,23,24]; consequently, therapy should be monitored most closely then. After the first few days, the monitoring test can usually be obtained daily.

Heparin-Induced Thrombocytopenia: Heparin can induce thrombocytopenia,[69–75] but recent studies[12–15] indicate that the frequency of heparin-induced thrombocytopenia (HIT) is < 1% when either unfractionated heparin or LMW heparin is given for no more than 5 to 7 days. Because of this finding, a platelet count should be checked between day 3 and day 5 of therapy. If heparin is administered for a longer period, another platelet count should be checked between day 7 and day 10 and another at day 14. The syndrome of HIT is unusual after 14 days of heparin therapy, although HIT complicated by thrombosis can sometimes develop after heparin therapy has been stopped. When the platelet count falls precipitously or in a sustained fashion, heparin therapy should be stopped. When the platelet count falls to < 100,000/μL, heparin therapy should be stopped. A marked fall in platelet count can signal antibody-mediated injury to platelets and endothelium. This syndrome may be associated with arterial thromboembolism and extension or recurrence of existing VTE.[76] If heparin therapy must be discontinued when the risk for recurrent embolism is great, many clinicians believe an inferior vena caval filter should be placed.

Table 2—*Body Weight-Based Dosing of IV Heparin**

APTT, s†	Dose Change, U/kg/h	Additional Action	Next APTT, h
< 35 (<1.2 × mean normal)	+ 4	Rebolus with 80 IU/kg	6
35–45 (1.2–1.5 × mean normal)	+ 2	Rebolus with 40 IU/kg	6
46–70‡ (1.5–2.3 × mean normal)	0	0	6§
71–90 (2.3–3.0 × mean normal)	−2	0	6
> 90 (> × mean normal)	−3	Stop infusion 1 h	6

*Initial dosing; loading, 80 IU/kg; maintenance infusion; 18 IU/kg/h (APTT in 6 h).

†The therapeutic range in seconds should correspond to a plasma heparin level of 0.2 to 0.4 IU/mL by protamine sulfate or 0.3 to 0.6 IU/mL by amidolytic assay. When APTT is checked at 6 h or longer, steady-state kinetics can be assumed.

‡Heparin, 25,000 IU in 250 μL D_5W. Infuse at rate dictated by body weight through an infusion apparatus calibrated for low flow rates.

§During the first 24 h, repeat APTT every 6 h. Thereafter, monitor APTT once every morning unless it is outside the therapeutic range.

Recombinant hirudin and danaparoid have become available for use in HIT. Recombinant hirudin (lepirudin) has been specifically approved for HIT accompanied by thrombosis. In this setting, lepirudin should be used for temporary anticoagulation and warfarin therapy delayed until the platelet count has risen to > 100,000/μL.[77] Details for treatment regimens of these new drugs are given in the chapter on mechanisms of action of heparin and LMW heparins.

Heparin use commonly leads to mild reductions in the level of circulating antithrombin III, and rarely, has been reported to induce disseminated thrombosis.[78] Long-term high-dose (4 months at 15,000 IU/d) heparin administration can lead to severe osteopenia.[79–83] In the rare patient with hypoaldosteronism, heparin may induce hyperkalemia.[84] Heparin causes mild asymptomatic elevation of liver enzyme levels in some patients between day 5 and day 10 of treatment.[85–88] These elevations either return to normal during treatment or following treatment without obvious untoward effect.

If a treatment dose of heparin is contraindicated for a patient with acute VTE, as it would be for someone with an actively bleeding CNS lesion, the acceptable alternative is insertion of a vena caval filter. Substitution of low-dose, prophylactic heparin or aspirin for full-dose heparin in this setting is ineffective.

1.2. Initial Anticoagulation With Heparin

Heparin is usually administered IV for 5 to 7 days in recovering patients. Unfortunately, such a short period of anticoagulation does not seem to interrupt completely the thrombotic process in many patients with proximal DVT. In one study, 10 to 14 days of conventional IV heparin therapy followed by low-dose subcutaneous heparin therapy did not adequately prevent recurrent VTE.[89] Consequently, most clinicians accompany the initial course of heparin with warfarin or another coumarin derivative for longer-term oral anticoagulation. The alternative is to give LMW heparin in a treatment dose[12–16,90,91] or give heparin in a larger subcutaneous dose that maintains the anticoagulated state for the full duration of treatment.[17,18,90,91]

The optimal duration of initial IV heparin therapy in patients with VTE appears to be 5 to 7 days, although therapy is sometimes prolonged in those with extensive disease (Table 3). Multiple randomized clinical trials in patients with proximal vein thrombosis indicate that when IV heparin is administered for 5 to 10 days and followed by adequate long-term anticoagulant therapy, the frequency of recurrent VTE is approximately 5%. The currently accepted approach is to begin heparin and oral anticoagulant therapy together at the time of diagnosis and to discontinue the heparin therapy between the fourth and seventh day. This approach seems to be effective and avoids an additional 4 to 5 days of subsequent hospitalization in many patients, greatly reducing the cost of initial therapy. Several randomized trials in patients with VTE have shown that 5 to 7 days of initial heparin therapy coupled with early warfarin initiation and treatment for at least 3 months is effective and safe.[12–16,69,70] It seems reasonable to recommend that heparin be given for 5 to 7 days and that warfarin be administered jointly with heparin for at least 4 to 5 days. Heparin therapy may then be discontinued when the prothrombin time yields an INR > 2.0 (Table 3).

LMW Heparin: Although continuous IV unfractionated heparin therapy is usually effective and safe, the regimen nearly always requires hospitalization with frequent monitoring and dose adjustment. LMW heparin as initial treatment of proximal vein thrombosis, which can be given without dose adjustment or laboratory monitoring, has lowered costs by allowing outpatient therapy in patients with DVT.[12,13] This approach to therapy has recently been reviewed.[92] Estimates of the number of hospital days that would be saved by outpatient administration of therapy average 5 to 6 days for each patient. Utilization of LMW heparin with a component of outpatient therapy could save approximately $250 million annually in the United States alone.[51–55,93] A recent publication[94] has given guidelines for selecting patients for outpatient therapy. Table 4 gives minimal requirements for outpatient treatment of VTE.

LMW fractions of heparin have a mean molecular weight of 4,000 to 5,000 d in contrast to unfractionated heparin, which has a mean molecular weight of 15,000 d.[95,96] The excellent bioavailability of LMW heparin, together with a longer plasma half-life[97–103] (as measured by anti-Xa activity) than unfractionated heparin, suggested that it would be possible to develop an effective regimen for initial treatment with LMW heparin using a once- or

Table 3—*Guidelines for Anticoagulation: Unfractioned Heparin**

Indication	Guidelines
VTE suspected	• Obtain baseline APTT, PT, CBC count • Check for contraindication to heparin therapy • Order imaging study, consider giving heparin 5,000 IU IV
VTE confirmed	• Rebolus with heparin 80 IU/kg IV and start maintenance infusion at 18 U/kg (see Table 2) • Check APTT at 6 h to keep APTT in a range that corresponds to a therapeutic blood heparin level (see text and Table 2) • Check a platelet count between days 3 to 5 • Start warfarin therapy on day 1 at 5 mg and adjust subsequent daily dose according to INR • Stop heparin therapy after at least 4 to 5 d of combined therapy when INR is > 2.0 • Anticoagulate with warfarin for at least 3 mo at an INR of 2.5; range; 2.0 to 3.0 (see Table 6)

*For subcutaneous treatment with unfractionated heparin, give 250 IU/kg subcutaneously q12h to obtain a therapeutic APTT at 6-8 h.
PT = prothrombin time.

twice-daily subcutaneous injection. The anticoagulant response (anti-Xa U/mL) observed with a given dose of LMW heparin was highly correlated with body weight,[102] and LMW heparin is effective in most patients when given in weight-based doses (anti-Xa U/kg body weight) without subsequent laboratory monitoring or dose adjustment.[12–16] All LMW heparins are cleared by the kidneys and caution should be exercised when the creatinine clearance is < 30 mL/min. The correct dose for massively obese persons has not been established, and laboratory monitoring (plasma anti-Xa activity) may be useful in such patients. Some authorities also recommend monitoring pregnant patients because the pharmacokinetics of LMW heparins appear to change during pregnancy, probably because of increased renal clearance of the drug.[104]

Studies in animal models of venous thrombosis have shown that some LMW fractions have equal (or greater) antithrombotic efficacy but less hemorrhagic effects than unfractionated heparin.[96,97,105–108] Whether this experimental observation applies clinically is uncertain,[105–107] since studies[12–16] have shown similar bleeding rates with unfractionated heparin and LMW heparin.

Multiple early randomized clinical trials[105,106,109–122] with differing end points compared LMW heparin with unfractionated heparin for the initial treatment of patients with venous thrombosis. Five studies[100,110,111,114,116] compared continuous IV LMW heparin with continuous IV unfractionated heparin, one trial[113] compared subcutaneous LMW heparin with subcutaneous unfractionated heparin, and four studies[115,117,123,124] compared subcutaneous LMW heparin with continuous IV unfractionated heparin. The results indicate that LMW heparin administered subcutaneously is as effective and safe as continuous IV heparin, but in the early studies,[109–122] conclusions of efficacy were largely based on venographic observations rather than clinical outcome.

LMW Heparin or Unfractionated Heparin? Several studies[12–16,123–130] have evaluated long-term clinical outcome using LMW heparin. Most studies[12–15,123–130] showed comparable outcomes when LMW heparin dosed subcutaneously without monitoring was compared with IV unfractionated heparin with monitoring and subsequent dose adjustment. One large study[124] showed lower rates of recurrence and bleeding when LMW heparin was compared to unfractionated heparin. Several meta-analyses[131,132] have also suggested that LMW heparin results in fewer episodes of recurrence and bleeding than unfractionated heparin. A small survival benefit may accrue to patients with malignancy and VTE who receive LMW heparin.[131,132]

Two studies[12,13] have shown that selected patients with proximal venous thrombosis can be treated at home with LMW heparin and warfarin therapy initiated together. When treatment is given at home, cost savings and improved quality of life are realized. In addition, selected patients can be discharged from the hospital early with a component of LMW heparin treatment at home.[12–16] While a few studies[123,124] suggested fewer recurrent events and less bleeding with LMW heparin, most studies[12–16,112–130] have not supported these findings in the treatment of VTE. Thus, the major advantages of LMW heparin in treatment appear to be convenience of administration and cost savings associated with home therapy or early hospital discharge.[132]

In summary, the LMW heparins used in these studies were at least equivalent to IV unfractionated heparin therapy. LMW heparin regimens offer the potential for treating selected patients with stable proximal DVT or PE in an outpatient setting and may offer particular benefit in those with malignancy. Not all patients with VTE are candidates for home treatment or early hospital discharge. The treating physician is best prepared to make these decisions (Table 4).

Accumulating evidence indicates that LMW heparin administered subcutaneously will largely replace IV unfractionated heparin therapy in the initial treatment of VTE. In most patients, subcutaneously administered LMW heparins do not require routine monitoring. Thrombocytopenia is uncommon enough that no more than one platelet count is recommended during a treatment period of 5 to 7 days. If therapy is prolonged > 7 days, subsequent platelet counts should be done.

Despite the care taken with meta-analysis, properties associated with one LMW heparin cannot always be extrapolated to a different LMW heparin, since treatment regimens differ somewhat for each drug. Table 5 gives recommendations for initiating treatment of DVT with LMW heparins that are approved for use in either the United States or Canada.

Treatment of VTE with LMW heparin has come of age. A large body of data for several of these products has been provided by well-designed clinical trials that featured clinically relevant end points. Estimates of treatment effect are available with acceptable confidence intervals. Treatment effects appear generalizable, *ie*, they apply to large populations of patients with VTE. Outpatient treatment of only a small minority of patients with VTE shifts overall costs of care in favor of LMW heparin. All of these findings argue strongly for use of LMW heparin in many patients with VTE.

Hirudin and Other Small Thrombin Inhibitors: Hirudin is the progenitor of a family of peptides that directly inhibit thrombin independent of an interaction with antithrombin. Because of this property, these peptides, particularly the smaller analogs, more effectively inhibit fibrin deposition in the interstices of a developing thrombus than does the larger heparin-antithrombin complex.[133] In experimental models of arterial and venous thrombosis, hirudin was more effective than heparin as an antithrombin.[134–136] These drugs also appear promising in clinical prophylaxis and treatment.[136,137] Recombinant hirudin (lepirudin) is available in the United States for treatment of HIT with thrombosis.[138] Argatroban, another direct thrombin inhibitor, has recently received US Food and Drug Administration approval in the United States.[139]

Coumarin Derivatives: These drugs are chemical derivatives of 4-hydroxycoumarin. They are well absorbed in the gut and transported in plasma bound to albumin. The drugs are metabolized by the liver and excreted in a

hydroxylated form in the urine. In North America, the predominant coumarin derivative in clinical use is racemic sodium warfarin.

Coumarins act in the liver by inhibiting the synthesis of four vitamin K-dependent coagulant proteins, factors II, VII, IX, and X, and at least two vitamin K-dependent anticoagulant factors, proteins C and S. The synthesis of other vitamin K-dependent proteins is also impaired, although the significance of this inhibition is uncertain since the function of other vitamin K-dependent proteins is largely unknown. The major mechanism of action is inhibition of a specific posttranslational event in protein synthesis: the γ-carboxylation of multiple glutamic acid residues near the amino terminus of the polypeptide chain. The failure of γ-carboxylation of glutamic acid residues markedly interferes with the function of the proteins by preventing calcium binding[140,141] and proper alignment of the activated factors on a phospholipid surface.[142] In the presence of coumarins, a number of analogous proteins are synthesized and released that not only are hypofunctional but also can interfere with normal coagulation reactions.[143,144] For this reason, plasma from patients receiving coumarin cannot be compared directly with dilutions of normal plasma or with plasma from individuals who congenitally lack vitamin K-dependent coagulation factors.

Coumarins require several days to achieve their full effect because time is required for normal coagulation factors to be cleared from plasma. This lag period varies according to the plasma clearance rates of the K-dependent factors, being shortest for factor VII and longest for factor II. Accordingly, the one-stage prothrombin time might appear adequately prolonged 24 h after a large loading dose of a coumarin derivative because of the relatively short half-life of factor VII, but plasma levels of the other three factors would still be high.[145] Moreover, proteins C and S, which have anticoagulant and fibrinolytic effects, are also vitamin K dependent. Protein C has plasma clearance kinetics similar to factor VII.[146] Therefore, by reducing effective protein C levels, a large loading dose of a coumarin derivative might tip the hemostatic balance toward coagulation rather than anticoagulation in the first 24 to 48 h of therapy. Animal studies and anecdotal clinical experience support the need for a period of overlap of heparin and warfarin therapy when treating acute VTE.[147–149] Early introduction of warfarin on day 1 or day 2 at a starting dose of 5 mg will usually keep the total duration of heparin therapy at no more than 7 days.[12–16,20,69,70,149,150] In this way, the incidence of HIT can also be minimized.

Table 4—*Minimal Elements for Early Discharge or Outpatient Therapy*

Responsible physician must ensure the following:
• Patient in stable condition with normal vital signs
• Low bleeding risk
• Absence of severe renal insufficiency
• Practical system for administration of LMW heparin and warfarin with appropriate monitoring
• Practical system for surveillance and treatment of recurrent VTE and bleeding complications

Monitoring Coumarin Therapy: Therapy is most commonly monitored with the one-stage prothrombin time.[151] When monitoring coumarin therapy, it is important to recognize that the heparin can be easily removed from plasma samples before performing the prothrombin time.[152,153] The clotting time is measured after mixing citrated plasma with calcium and a well-characterized tissue thromboplastin. Commercially available tissue thromboplastins vary in their sensitivity to the warfarin effect. Consequently, prothrombin times performed with different thromboplastins are not always directly comparable,[154] which has resulted in much confusion over the years as to the intensity of the anticoagulant effect required. This problem has been substantially alleviated with widespread adoption of the INR and use of thromboplastins with international sensitivity index values near 1.0. It also appears that using a 3.2% citrate tube filled to the full volume is important to help standardize the INR.[155] Another major difficulty with coumarin therapy is the number of factors that influence coumarin metabolism and action. A complete review of these factors is beyond the scope of this chapter. These interactions have been reviewed recently.[156] Ideally, a patient treated with warfarin should be receiving as few other drugs as possible, should use alcohol not at all or only moderately, and should be consuming a diet that contains a consistent amount of vitamin K.[157]

Intensity of Coumarin Therapy: As with heparin, a threshold effect of warfarin seems necessary to achieve the antithrombotic state.[36,37] Evidence from multiple studies over the last decade indicates that effective therapy in VTE is reflected by an INR of 2.0 to 3.0.[12–16,20,69,70,158,159] These studies demonstrated that anticoagulation with warfarin to an INR of 2.0 to 3.0 results in fewer bleeding complications yet protects adequately against recurrent thromboembolism. In treating VTE or preventing it in higher-risk patients, the recommended therapeutic range for the prothrombin time is an INR of 2.0 to 3.0 with a target of 2.5.[160]

1.2 Long-term Anticoagulation

The duration of anticoagulation for VTE must be tailored to the individual patient. In selected patients whose risk factors can be interrupted, *eg*, pharmacologic estrogen use or transient immobilization, < 3 months of therapy may be sufficient, although adequate clinical trials should be performed validating this brief a duration of therapy before such a recommendation is made.[161–164] Patients with slowly resolving risk factors, *eg*, prolonged immobilization, should be treated for at least 3 months. Patients with cancer, antiphospholipid syndrome, deficiency of antithrombin III, or recurrent VTE from any cause should be treated for longer periods. Patients with homozygous factor V Leiden or multiple thrombophilic states should probably be treated for longer periods.

Table 5—*Guidelines for Anticoagulation With LMW Heparin*

Indications	Guidelines
VTE suspected	• Obtain baseline APTT, PT, CBC • Check for contraindication to heparin therapy • Order imaging study, consider giving unfractionated heparin 5,000 U IV or LMW heparin
VTE confirmed	• Give LMW heparin (dalteparin*, enoxaparin†, nadroparin‡, tinzaparin§) • Start warfarin therapy on day 1 at 5 mg and adjust the subsequent daily dose according to INR • Check a platelet count between days 3 to 5 • Stop LMW heparin therapy after at least 4 to 5 d of combined therapy when INR is > 2.0 • Anticoagulate with warfarin for at least 3 months at an INR of 2.5, range of 2.0–3.0 (see Table 6)

*Dalteparin sodium 200 anti-Xa IU/kg/d subcutaneously. Single dose should not exceed 18,000 IU. (approved in Canada). PT = prothrombin time.

†Enoxaparin sodium 1 mg/kg q12h subcutaneously or enoxaparin sodium 1.5 mg/kg/d subcutaneously. Single daily dose should not exceed 180 mg (approved in both the United States and Canada).

‡Nadroparin calcium 86 anti-Xa IU/kg bid subcutaneously for 10 days (approved in Canada) or nadroparin calcium 171 anti-Xa IU/kg subcutaneously daily. Single dose should not exceed 17,100 IU.

§Tinzaparin sodium 175 anti-Xa IU kg/d subcutaneously daily (approved in Canada and the United States).

Patients who are heterozygous for factor V Leiden should receive at least 3 months of treatment following a first event (Table 6).

In an early controlled trial that addressed duration, 2 weeks of adequate anticoagulation was not sufficient.[89] However, trials[21,165–167] comparing shorter periods of therapy (3 to 6 months) with longer periods (> 6 months) always demonstrated lower recurrence rates with the longer periods of treatment, a benefit that accrued mostly to patients with idiopathic thrombosis. Thus, the strongest support for extended duration of treatment applies to those with idiopathic thrombosis, who should be treated with anticoagulant drugs for at least 6 months after a first episode. More studies are needed to identify specific patients who need long-term treatment. One trial in patients who had suffered two separate events showed reduced recurrence with prolonged anticoagulation (> 2 years).[21] Benefit again occurred predominantly in patients with idiopathic venous thrombosis, but it was partially offset by increased bleeding associated with longer therapy.[21] Table 6 offers recommendations for length of therapy based on underlying risk for recurrence. In this regard, one should remember that a very important risk factor for recurrent VTE is a prior event. Increasing age is also an important risk factor and should be considered when determining length of therapy. These recommendations are of grade C quality because to our knowledge, there have been no controlled trials of duration of therapy in most of the acquired or hereditary conditions listed in Table 6. A number of trials are in progress, and new information will be forthcoming. However, patients with any of these conditions are known to be at higher risk for recurrence than are those with reversible or time-limited risk factors, and it is reasonable, although unproved, to recommend longer periods of therapy.[21]

Complications: The major complication associated with warfarin use is hemorrhage.[163,164] The risk of bleeding is related to prolongation of the INR. There is now abundant evidence that bleeding, but not efficacy, is reduced when the therapeutic range is reduced from an INR of 3.0 to 4.5 to an INR of 2.0 to 3.0. To minimize bleeding, investigators have sought to find the lowest effective level of anticoagulation, and current evidence strongly supports the concept that anticoagulation for VTE above an INR of 3.0 is generally unnecessary.[158,159,166–176] One possible exception to this statement appears to be patients with the antiphospholipid antibody syndrome who may require a higher INR.[148,177] Any vascular site in the body can bleed with coumarin therapy, but many observers have been impressed by the frequency with which localized organic lesions (tumors, ulcers, cerebral aneurysms) bleed following induction of anticoagulant therapy. If clinically indicated, the effects of warfarin effects can be corrected within 24 h by administration of vitamin K. Serious bleeding can be treated with fresh frozen plasma. Less serious bleeding associated with a modest elevation of the INR can generally be treated by withholding warfarin therapy or giving small doses (1 to 2 mg) of oral or subcutaneous vitamin K.[178]

Much is made of the bleeding complications associated with heparin and warfarin, but it is important to remember the high mortality and morbidity rates associated with untreated and undertreated VTE.[6–9]

Another complication associated with the coumarins is a vascular purpura that causes skin necrosis and occurs occasionally in the first weeks of therapy.[179–181] This complication has been associated with protein C deficiency and malignancy.[182–184] Coumarins cross the placenta and cause spontaneous abortion and specific embryo abnormalities if administered in the first trimester of pregnancy.[185–186] Therefore, warfarin must not be administered during pregnancy, and all women of childbearing potential receiving warfarin must avoid becoming pregnant. The long-term therapy of choice in pregnant women is a treatment dose of LMW heparin or unfractionated heparin given subcutaneously in an adjusted dose to prolong the APTT to a range that corresponds to a plasma heparin level of 0.2 to 0.4 IU/mL for most of the dosing interval. Warfarin is administered routinely in the postpartum period, even to nursing mothers, since the drug metabolite excreted in breast milk is not an anticoagu-

lant.[187,188] Patients who develop VTE during pregnancy should receive postpartum therapy with warfarin for at least 6 weeks.[189]

Cost-Effectiveness of Anticoagulant Therapy: Cost-effective anticoagulant therapy should arrest thrombosis and prevent recurrent VTE, have a low incidence of bleeding and other complications, and be convenient and inexpensive to administer. An early cost-effectiveness analysis[190] ranked several anticoagulant regimens. These regimens all began with a 10- to 14-day course of IV heparin followed by various long-term regimens. In this analysis, warfarin therapy (INR 2.0 to 3.0) was most cost-effective for long-term anticoagulation in most patients with VTE. Adjusted-dose subcutaneous heparin or LMW heparin would be the long-term treatment of choice for pregnant patients and those with hypersensitivity to warfarin, or when laboratory facilities are inadequate to monitor warfarin therapy. In some settings, home monitoring of warfarin therapy might afford additional savings.

More recently, LMW heparin combined with early initiation of warfarin therapy promises to be the most cost-effective therapy because many patients can be treated without hospitalization or with very short inpatient stays.[12–16] In many locales, this statement already applies to both inpatient and outpatient treatment.[51–55] Since the price of LMW heparins has begun to fall, it is expected that statements favoring cost-effectiveness of these drugs will become even more generalizable.

Table 6—*Duration of Therapy

3 to 6 mo	• First event with reversible† or time-limited risk factor (patient may have underlying Factor V Leiden or prothrombin 20210)
≥ 6 mo	• Idiopathic VTE, first event
12 mo to lifetime	• First event‡ with ▶ Cancer, until resolved ▶ Anticardiolipin antibody ▶ Antithrombin deficiency • Recurrent event, idiopathic or with thrombophilia

*All recommendations are subject to modification by individual characteristics including patient preference, age, comorbidity, and likelihood of recurrence.

†Reversible or time-limited risk factors: surgery, trauma, immobilization, estrogen use.

‡Proper duration of therapy is unclear in first event with homozygous factor V Leiden, homocystinemia, deficiency of protein C or S, or multiple thrombophilias; and in recurrent events with reversible risk factors.

2. Thrombolytic Therapy

Thrombolytic agents dissolve thrombi by activating a zymogen, plasminogen, to the active agent, plasmin. Plasmin, when in proximity to a thrombus or a hemostatic plug, degrades fibrin to soluble peptides.[191] Circulating plasmin also degrades soluble fibrinogen and, to some extent, several other plasma proteins. Streptokinase, urokinase, and tissue plasminogen activator (alteplase [tPA]) are the thrombolytic agents currently approved for clinical use in VTE.

Both streptokinase and urokinase have similar thrombolytic effects as judged by large clinical trials in PE.[192,193] Using paired angiographic comparisons in each patient, resolution of thromboembolus, seen with 12 h or 24 h of urokinase therapy or 24 h of streptokinase therapy, was comparable at 24 h and was approximately three times that seen with heparin alone. Pulmonary vascular resistance was also reduced at 24 h by 35% compared with 4% in the heparin group. Whereas initial lung scan improvement was greater in the thrombolytic group at 1 day and 3 days, subsequent scan improvement was similar in the two groups. Twelve hours of urokinase therapy had equivalent thrombolytic efficacy to 24 h of streptokinase therapy, and these are the recommended infusion times for PE.[194] tPA has comparable thrombolytic capacity to urokinase and streptokinase and can be administered for shorter duration.[195]

The use of thrombolytic therapy in the treatment of DVT and PE remains highly individualized. In treatment of DVT, early use of a thrombolytic agent such as streptokinase can decrease subsequent pain, swelling, loss of venous valves, and in some studies has reduced incidence of the postphlebitic syndrome.[196–200] However, this syndrome is notoriously slow and variable in its development, and conflicting findings[201,202] mandate that further long-term controlled studies be performed. For PE, thrombolytic therapy followed by heparin clearly achieves more rapid resolution of thromboembolus compared with heparin alone. Thrombolytic agents also result in superior early resolution of lung scan abnormalities and more rapid hemodynamic improvement. With careful selection of patients, it has become evident that the incidence of hemorrhage can be greatly decreased from that seen in the early trials. However, patients with VTE who receive thrombolytic therapy have a 1 to 2% risk of intracranial bleeding. Furthermore, there is as yet no clearly established short-term mortality effect with a thrombolytic agent in PE.[203] This finding is not surprising, since previous trials were mostly designed primarily to establish the thrombolytic effects of these agents. The low all-cause mortality at 3 months (< 10%) of patients treated with heparin and warfarin has always precluded the identification of a mortality effect of thrombolytic therapy when a relatively small number of patients are studied. Studies[1,12–16,204] have shown that when PE is promptly diagnosed and properly treated, subsequent mortality directly due to PE is about 2%. Because of the favorable results with heparin and warfarin, thrombolytic therapy should usually be reserved for the treatment of patients with acute massive embolism who are in hemodynamically unstable condition and do not seem prone to bleeding. Confirmatory evidence is needed before one can state that thrombolytic therapy decreases the incidence of long-term disability after massive PE. These drugs may also offer benefit to younger patients with massive ileofemoral thrombosis. Epidemiologic studies must also determine the prevalence and risk factors for subsequent chronic thromboembolic pulmonary hypertension in adequately anticoagulated patients with acute PE.

In patients with DVT, urokinase and streptokinase are approved for 48 to 72 h of therapy, but in practice, regimens are quite variable, particularly when therapy is administered by catheter-directed infusion as is favored by radiologists. In PE, 12 h of urokinase treatment proved as effective as 24 h of either urokinase or streptokinase treatment, and 2 h of tPA treatment appears to be as effective as any of the older regimens.[205–207] The question of duration of therapy can be answered only by controlled studies comparing standard and shorter courses of thrombolytic therapy.[208–210]

All thrombolytic agents are administered IV in dosing regimens that are designed to activate fibrinolysis systemically in > 90% of patients. The regimens will achieve thrombolysis throughout the vasculature. Although tPA and reteplase are somewhat more fibrin specific than streptokinase and urokinase, all of these agents have the potential to lyse a fresh platelet-fibrin plug anywhere in the vasculature and cause bleeding at that site. For PE, streptokinase is recommended in a 250,000-IU loading dose followed by 100,000 IU/h for 24 h. Urokinase is recommended in a 4,400 IU/kg body weight loading dose followed by 2,200 IU/kg/h for 12 h. For PE, tPA is recommended in a 100-mg infusion over 2 h. Reteplase is not currently approved in the United States for treatment of VTE, but this agent shows promise for rapid thrombolysis.[211] The drug is given in two separate IV boluses of 10 U approximately 30 min apart. For treatment of DVT, streptokinase should be given in the same manner as for PE, but the duration of therapy should probably be lengthened. Heparin should not be infused concurrently with streptokinase or urokinase. For tPA or reteplase, concurrent use of heparin is optional.

Infusion of a thrombolytic agent directly onto a venous thrombus has never been convincingly shown to be superior to infusion of the agent through a peripheral vein. There is little correlation between *in vitro* tests of fibrinolysis, on one hand, and thrombolysis or bleeding, on the other hand. This statement is particularly true for tPA and reteplase, but applies to streptokinase and urokinase as well. Consequently, when streptokinase or urokinase is infused, a thrombin time or APTT may be monitored 2 to 4 h into treatment. Prolongation of either test by 10 s indicates activation of fibrinolysis. Further laboratory monitoring of therapy is unnecessary. No laboratory monitoring of tPA or reteplase therapy is recommended. After thrombolytic therapy is completed, IV heparin therapy can be restarted once the thrombin time or APTT is shown to be less than two times normal.

Beside the lack of a proven mortality effect, thrombolytic therapy of VTE differs from therapy of myocardial infarction in another way. In myocardial infarction, thrombolytic therapy appears to dissolve the coronary thrombus in most cases, but in VTE, particularly PE, complete dissolution of thrombus is the exception.[192–195] Partial dissolution is the rule because venous thromboemboli are older, larger, and more organized than coronary thrombi. Since no currently available agent or regimen usually dissolves the VTE completely, interest has turned to smaller doses and shorter duration of therapy in an effort to achieve the desired clinical effect with less bleeding. It is not yet clear that these regimens will cause less bleeding, but they appear to effect comparable thrombus resolution to regimens of longer duration.[210,211] The optimum application of thrombolytic therapy for PE remains in doubt, with some authorities arguing for treatment of only those in shock[212] and others who would enlarge treatment indications to include those with echocardiographic evidence of right ventricular dysfunction.[213]

3. Inferior Vena Caval Procedures

The major rationale for inferior vena caval filters is the presence of a contraindication or complication of anticoagulation in an individual with or at high risk for proximal vein thrombosis of the lower extremity. Less frequent indications include recurrent thromboembolism despite adequate anticoagulation, massive hemodynamically pulmonary embolism, chronic recurrent embolism with pulmonary hypertension, and the concurrent performance of surgical pulmonary embolectomy or pulmonary endarterectomy.

The most popular method of inferior vena caval interruption is placement of a filter developed by Greenfield and Rutherford.[214] This six-legged device can be inserted through the internal jugular vein or femoral vein, and advanced into place in the inferior vena cava using fluoroscopic or ultrasonic guidance. In several large series,[214–216] the long-term patency rate of the filter has been 98%. Most authorities recommend resumption of anticoagulation as soon as possible after insertion of a filter because the filter alone is not an effective treatment of VTE. Results and complications with various filters have been summarized.[217] The bird's nest filter also appears to be effective.[218,219] However, results with the L-G medical filter and the Gunther filter appear to be less satisfactory.[220–222] Some authorities consider venous anatomic abnormalities, pregnancy, and thrombus proximal to the intended point of placement to be contraindications to filter insertion. Suprarenal placement of filters has been safe and effective.[223] The ease of insertion and low complication rates of the new filters have increased the use of these devices. Filters have been placed with ultrasound guidance at the bedside of critically ill patients.[224] Temporary filters are currently undergoing testing.[225] Superior vena caval filters have been placed in patients with upper-extremity DVT.[226]

Vena caval filters have been used for primary prophylaxis of thromboembolism in patients at high risk to bleed, including patients with extensive trauma, visceral cancer, and those undergoing hip and knee surgery.[214,227-237] These studies are uncontrolled case series, and many of them are weakened by incomplete reporting of patient outcomes. In the only (to our knowledge) randomized study[238] of filter placement, the device did not prolong early or late survival in patients after a first episode of VTE, although it did reduce the rate of PE. This benefit was offset by a tendency for more recurrent DVT in those patients who received a filter.

4. Pulmonary Embolectomy

Pulmonary embolectomy continues to be performed in emergency situations when more conservative measures

have failed. If it is attempted, there is general agreement that a candidate meet the following criteria: (1) massive PE (angiographically documented if possible); (2) hemodynamic instability (shock) despite heparin and resuscitative efforts; and (3) failure of thrombolytic therapy or a contraindication to its use. Operative mortality in the era of immediately available cardiopulmonary bypass has ranged from 10 to 75% in uncontrolled retrospective case series.[239-241] In patients who have suffered cardiopulmonary arrest, mortality has been reported between 50% and 94%. In a recent series of 96 patients (55% of whom did not meet the criteria of hemodynamic instability), univariate analysis identified cardiac arrest and shock as predictors of mortality, and multivariate analysis confirmed the significance of cardiac arrest and underlying cardiopulmonary disease as predictors of mortality.[242] Reported postoperative complications include ARDS, mediastinitis, acute renal failure, and, of particular concern, severe neurologic sequelae. Pulmonary embolectomy should be considered when a patient meets the above criteria and an experienced cardiac surgical team is immediately available.[239-242]

5. Catheter Transvenous Extraction or Fragmentation of Emboli

A cap device has been developed that fits over an 8.5F double-lumen, balloon-tipped steerable catheter to permit suction extraction of PE under fluoroscopy with ECG monitoring.[243] In a series of 26 patients undergoing catheter embolectomy, extraction was successful in 23 patients, with a mortality rate of 27%.[244] Two patients subsequently underwent open embolectomy. Over the same time in the same institution, six patients had open embolectomy for acute PE with a mortality of 33%.[244] A report of catheter embolectomy in 18 patients with a 28% mortality rate has also been published.[245]

More recently, a catheter system has been devised that fragments thromboemboli by generating a Venturi effect at the catheter tip using jets of high-speed saline solution. The fragmented thrombus is then evacuated through the catheter lumen. This device looks promising, but there has been insufficient experience with it to make firm recommendations for its use.[246] Another approach is to use a combination of pharmacologic and mechanical thrombolysis.[247]

In severely ill patients who may be candidates for catheter extraction or dissolution or for surgical embolectomy, echocardiography may provide rapid bedside diagnosis and hasten therapeutic interventions.[248]

6. Paradoxical Embolism

The frequency of stroke and systemic embolism that is associated with VTE remains unknown. The complication most frequently occurs through a patent foramen ovale.[249] Echocardiography is a useful diagnostic tool when paradoxical embolism is suspected.[250] Patency of the foramen ovale should be suspected when stroke is cryptogenic or occurs in younger people. Thrombolytic therapy may be useful as acute therapy in some patients with paradoxical embolism.[251] Recently, percutaneous closure of patent foramen ovale has been demonstrated.[252]

7. Chronic Pulmonary Thromboembolism and Pulmonary Hypertension

A few individuals with PE (probably $< 2\%$) do not resolve the process and subsequently develop pulmonary hypertension. Although primary pulmonary hypertension and chronic thromboembolic pulmonary hypertension demonstrate similar histologic appearances in the microscopic pulmonary vessels,[253] in the latter condition, the primary disorder is most likely obstruction of macroscopic pulmonary arteries by unresolved, organized emboli.[254] If the obstructing lesions are sufficiently proximal, chronic thromboembolic pulmonary hypertension may be amenable to pulmonary thromboendarterectomy (PTE).[255] The syndrome should be considered in anyone with unexplained dyspnea on exercise, even if pulmonary function tests reveal mild restriction.[256] The most important preliminary diagnostic test is the pulmonary perfusion scan, which nearly invariably discloses perfusion defects, although the size of the perfusion defects frequently underestimates the extent of disease.[257] This finding contrasts with scan findings in primary pulmonary hypertension in which perfusion defects, if present, are minimal. With an experienced surgical and medical team, surgical endarterectomy has been shown to result in significant relief of pulmonary hypertension and disability.[258]

Randomized, controlled clinical trials of PTE for patients with chronic thromboembolic pulmonary hypertension have not been performed because there is no reasonable alternative treatment. However, a recent cross-sectional survey[259] of 308 patients evaluated at 1 year after PTE disclosed dramatic improvements in functional status and quality of life.

8. Primary Pulmonary Hypertension

There continues to be interest in treating primary pulmonary hypertension with antithrombotic or fibrinolytic agents,[260-262] although to our knowledge, there have been no randomized trials evaluating such therapies in this condition. However, the use of warfarin in patients who did not respond to calcium channel blockers appeared to result in improved survival.[263] A prospective controlled study continues to be needed to confirm this observation.

Recommendations

1. Treatment of VTE

1.1. Effective Regimens

1.1.1. We recommend that patients with DVT or PE should be treated acutely with LMW heparin, unfractionated IV heparin, or adjusted-dose subcutaneous heparin (all grade 1A).

1.1.2. When unfractionated heparin is used, we recommend that the dose should be sufficient to prolong the APTT to a range that corresponds to a plasma heparin level of 0.2 to 0.4 IU/mL by protamine sulfate or 0.3 to 0.6 IU/mL by an amidolytic anti-Xa assay (grade 1C+).

1.1.3. In comparison to unfractionated heparin, LMW heparin offers the major benefits of convenient dosing and facilitation of outpatient treatment. LMW heparin treatment may result in slightly less recurrent VTE and may offer a survival benefit in patients with cancer. We recommend that clinicians use LMW heparin over unfractionated heparin (grade 2B).

1.2. Initial Anticoagulation With Heparin

1.2.1. We recommend that treatment with heparin or LMW heparin should be continued for at least 5 days and that oral anticoagulation should be overlapped with heparin or LMW heparin for at least 4 to 5 days (grade 1A in comparison with treatment for 10 days).

Remark: For most patients, treatment with warfarin can be started together with heparin or LMW heparin. The heparin product can be discontinued on day 5 or day 6 if the INR has been therapeutic for 2 consecutive days.

1.2.2. For massive PE or severe iliofemoral thrombosis, we recommend a longer period of heparin therapy of approximately 10 days (grade 1C).

1.3. Long-term Anticoagulation

1.3.1. We recommend that oral anticoagulant therapy should be continued for at least 3 months to prolong the prothrombin time to a target INR of 2.5 (range, 2.0 to 3.0). When oral anticoagulation is either contraindicated or inconvenient, a treatment dose of LMW heparin or unfractionated adjusted-dose heparin to prolong the APTT to a time that corresponds to a therapeutic plasma heparin level for most of the dosing interval should be used (grade 1A).

1.3.2. We recommend that patients with reversible or time-limited risk factors should be treated for at least 3 months (grade 1A).

1.3.3. We recommend that patients with a first episode of idiopathic VTE should be treated for at least 6 months (grade 1A).

1.3.4. For patients with recurrent idiopathic VTE or a continuing risk factor such as cancer, antithrombin deficiency, or anticardiolipin antibody syndrome, we recommend treatment for 12 months or longer (grade 1C).

Remark: Duration of therapy continues to be individualized in patients with deficiency of proteins C or S, multiple thrombophilic conditions, homocystinemia, and homozygous factor V Leiden.

1.3.5. We recommend that symptomatic isolated calf vein thrombosis should be treated with anticoagulation for at least 6 to 12 weeks (grade 1A). If for any reason anticoagulation is not administered, we recommend that serial noninvasive studies of the lower extremity should be performed over the next 10 to 14 days to assess for proximal extension of thrombus (grade 1C).

2. Thrombolytic Therapy

Remark: The use of thrombolytic agents in the treatment of VTE continues to be highly individualized, and clinicians should have some latitude in using these agents. In general, patients with hemodynamically unstable PE or massive iliofemoral thrombosis, who are at low risk to bleed, are the most appropriate candidates.

3. Inferior Vena Caval Procedures

3.1. We recommend placement of an inferior vena caval filter when there is a contraindication or complication of anticoagulant therapy in an individual with or at high risk for proximal vein thrombosis or PE (grade 1C+). We also recommend placement of an inferior vena caval filter for recurrent thromboembolism that occurs despite adequate anticoagulation, for chronic recurrent embolism with pulmonary hypertension, and with the concurrent performance of surgical pulmonary embolectomy or pulmonary thromboendarterectomy (grade 1C).

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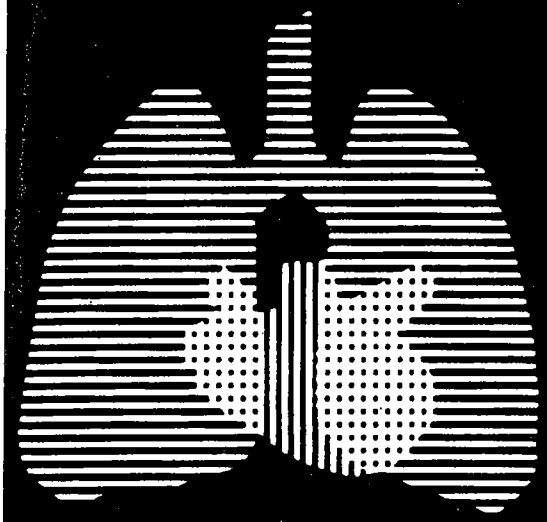

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